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REVIEW ARTICLE

Evidence-based radiology (part 2): Is there sufficient research to support the use of therapeutic injections into the peripheral joints?

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Abstract
Introduction This review article addresses the best evidence currently available for the effectiveness of injection therapy for musculoskeletal conditions involving the peripheral joints. The research is presented by anatomical region and areas of controversy and the need for additional research are identified.
Discussion Randomized controlled trials, meta-analyses and systematic reviews are lacking that address the effectiveness of therapeutic injections to the sternoclavicular, acromioclavicular, ankle and foot joints. No research studies of any kind have been reported for therapeutic injections of the sternoclavicular joint. With the exception of the knee, possibly the hip and patients with inflammatory arthropathies, research does not unequivocally support the use of therapeutic joint injections for most of the peripheral joints, including the shoulder. Additionally, controversy exists in some areas as to whether or not corticosteroids provide better outcomes compared to local anesthetic injections alone.
Conclusion When viscosupplementation injections are compared to corticosteroids in patients with osteoarthritis of the knee, the evidence supports the use of viscosupplementation for more prolonged improvement in outcomes, with corticosteroids being good for short-term relief.

Keywords Therapeutic injections · Joint injections · Corticosteroid injections · Viscosupplementation · Therapeutic joint injections

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Introduction

Amongst the most common conditions presenting to primary health care practitioners are those involving the musculoskeletal system. Treatment of these various conditions is often costly with the effectiveness of many of the treatments not necessarily substantiated according to the criteria of evidence-based medicine. Conservative care is provided to most patients initially, consisting of several options such as exercise, educational interventions, manipulation or mobilization, various physical therapy treatments, or pharmacological interventions [1]. If conservative measures fail to alleviate the symptoms, many patients are then referred for imaging-guided diagnostic or therapeutic joint injections. The purpose of a diagnostic joint injection is to determine whether or not a particular joint is the source of the patient's complaint. This injection delivers a local anesthetic with a particular length of action with the patient response compared to the expected action of the anesthetic. Therapeutic joint injections add a corticosteroid in addition to the local anesthetic to address any inflammation occurring and prolong the therapeutic effect [2–6].

A search of the literature was performed, focusing primarily on systematic reviews, meta-analyses and randomized controlled clinical trials (RCTs) to evaluate the level of evidence concerning the effectiveness of therapeutic joint injections into the various peripheral joints of the extremities, identify best practice and to determine specific areas where further research is needed. Retrospective and prospective cohort studies and case series studies were included in the absence of other evidence. The search strategy utilized PubMed, including the 'links' and 'limits' functions specifically for reviews, meta-analyses, randomized controlled trials and clinical trials.

Additionally, the Cochrane database, Google scholar and references for articles retrieved were searched.

Systematic reviews, meta-analyses and high quality RCTs are considered by the traditional scientific community as 'best evidence' and therefore exclude evidence from practical experience, expert opinion, cohort studies and guidelines. Therefore, the conclusions drawn from this 'best evidence' approach may not reflect positively on some commonly performed therapeutic injections. This indicates an interest for further research studies, along with perhaps reconsideration as to what indeed constitutes 'best evidence' in interventional pain management.

Upper extremity

This review will focus little on the use of therapeutic corticosteroid injections for the inflammatory arthropathies, particularly rheumatoid arthritis (RA) and juvenile chronic arthritis, as the evidence in support of this treatment, at least for short term improvement, is fairly strong [7–10]. Table 1 summarizes the research implications for therapeutic joint injection of the extremities.

Shoulder (glenohumeral joint and subacromial injections)

In spite of the fact that therapeutic corticosteroid injections are commonly used to treat a variety of shoulder conditions, including tendinopathies, bursitis, impingement syndrome, adhesive capsulitis, rotator cuff tears and arthritis, two systematic reviews and two recent meta-analyses found limited evidence to support the effectiveness of this treatment [11–14]. Problems include heterogeneity in the methods used as well as small sample sizes [11].

Two areas where these therapeutic shoulder injections may be effective include subacromial injection for rotator cuff disease (tendinopathy) and intra-articular injection for adhesive capsulitis. However, the evidence supporting the use of steroids for these conditions remains controversial [12, 13], especially for long-term improvement. For rotator cuff disorders, corticosteroids appeared less effective for function than other treatments combined, and appear to be no more effective than NSAIDs (non-steroidal anti-inflammatory drugs) [12] and local anesthetics [15], even with longer-term follow-up. One problem with the assessment of the effectiveness of shoulder injections is the common lack of a specific diagnosis. Distinguishing a rotator cuff tear from a tendinopathy is important as there is little evidence to support therapeutic injections for tears [12, 13], but some evidence to support their use for tendinopathy [14]. A meta-analysis done in 2005 on subacromial injections for rotator cuff tendinitis reported that the numbers needed to treat ranged from 1.4–2.2 patients [14].

Shoulder (acromioclavicular joint)

No systematic reviews, meta-analyses or RCTs were found on therapeutic injections for the acromioclavicular (AC) joint. One recent prospective cohort study with a 5-year follow-up was found however that investigated this procedure on patients with primary AC joint arthritis [16]. This group of researchers reported that injection of corticosteroid into the AC joint is an effective treatment for primary isolated osteoarthritis (OA) and that this improvement of approximately 25% reduction in symptoms lasts at least 12 months. Although the therapeutic effect diminished over time, benefit was felt for up to 5 years. This study highlights the importance of having a specific diagnosis in order to determine which patients (i.e. subgroups) may benefit from a particular procedure. While only patients with osteoarthritis were included in this study, the results are meaningful to physicians and patients with this diagnosis in making treatment decisions. Similarly, a larger prospective cohort study on patient responses to a single therapeutic AC joint injection looked at specific AC abnormalities associated with AC osteoarthritis as visualized on MR images and compared these abnormalities with patient responses to injection. Specific abnormalities associated with a better patient response included hypertrophy of the joint capsule and osteophytes projecting inferiorly from the joint [17]. However, pain response was only measured at one time point, 15 min post injection. No conclusions can be made about long-term effectiveness. Finally, a third prospective cohort study on patients with osteoarthritis of the AC joint found that both pain and shoulder range of motion improved after a single injection of corticosteroid to the joint [18]. Again this study only looked at short-term outcomes with improvement still evident at 2 weeks post injection.

Shoulder (sternoclavicular joint)

No investigations on therapeutic injections targeting the sternoclavicular joint were found, although this procedure is referred to in papers outlining treatment options for joint pain. While the sternoclavicular joint is not a common source of pain compared to the other joints of the shoulder region, it would be worthwhile to begin to establish outcomes on patients receiving this treatment.

Elbow-lateral epicondylitis

A meta-analysis done in 2008 looked at 20 RCTs investigating the effectiveness of corticosteroid injections for the treatment of shoulder and elbow tendinopathy [12]. As reported for the shoulder, there is evidence of the short-term effectiveness (1–3 weeks and 4–8 weeks) of these injections for tendonitis, but at longer term follow-up,

Table 1 Summary of therapeutic corticosteroid injections into peripheral joints

Joint	Conditions treated	Evidence	Research follow-up
Shoulder (glenohumeral region)	Adhesive capsulitis Rotator cuff tendinopathy	Controversial Small effects and of short duration Little evidence for complete rotator cuff tears	Is the steroid needed? Specific diagnoses needed prior to treatment. Larger sample sizes needed. Compare duration of symptoms prior to injection with outcome
Acromioclavicular	Osteoarthritis	Limited due to few studies, but promising for OA	Larger sample sizes needed. More long-term follow-up studies on patients with specific findings on MRI that may be linked with pain
Sternoclavicular	?	No evidence	Start to investigate this joint
Elbow	Lateral epicondylitis	1 recent Meta-analysis. May be effective for short-term pain relief, but no better than NSAIDs. Worse for functional outcomes in the long term	Does the specific corticosteroid make a difference in outcomes? Comparison studies with less invasive treatments.
Wrist	Carpal tunnel syndrome	Systematic review supports steroid injections as superior to other forms of treatment for up to 1 month for patients with mild to moderate symptoms	More RCTs comparing steroid injections with splint plus NSAIDs or Helium-Neon laser treatments for long-term results
Hand/Wrist	Stenosing tenosynovitis (de Quervain's)	Only descriptive studies done, or RCTs in which all groups received steroid injection. Steroid injection alone appears to be the superior treatment	Comparative studies between steroids and other treatments need to be done
1st CMC	Osteoarthritis	One good RCT comparing viscosupplementation injection to steroid. Viscosupplementation was far superior at 6-month follow-up. Steroid provided faster but short-term pain relief, maximum at 2–3 weeks post injection	More comparative studies are needed
Hip	Osteoarthritis	3 RCTs. As in other joints, steroids provide short-term pain relief, particularly night pain. Viscosupplementation injections appear to be effective.	Frequency and number of injections needs to be addressed. More comparisons studies are needed, particularly involving viscosupplementation
Knee	Osteoarthritis	3 recent systematic reviews + 1 meta-analysis. Steroids effective for short term pain relief. Triamcinolone superior to betamethasone. Viscosupplementation is effective for pain relief, function and global improvement	More direct product comparison studies are needed for viscosupplementation drugs
Ankle	Osteoarthritis	Minimal evidence. 1 recent prospective small cohort study. Significant improvement in Foot and Ankle Outcome Score at 6-month follow-up.	More comparative and prospective cohort studies needed. Longer term follow-up. Comparison of steroid with viscosupplementation
1st MTP	Osteoarthritis	Minimal evidence. 1 RCT compared viscosupplementation with corticosteroid injections. Both significantly reduced pain. Viscosupplementation was superior, particularly for longer term relief as well as pain on walking	One well designed RCT is planned. More are needed, along with prospective cohort studies on large patient numbers

steroid injections were inferior to other treatments for function. Additionally, NSAIDs were just as effective as steroid injections for improvement in the short term.

Three RCTs published after the meta-analysis was conducted provide more insight into the use of corticosteroid injections for lateral epicondylitis. For patients wishing an early return to activities such as high level athletes, an injection of a steroid plus local anesthetic provided better relief compared to physiotherapy treatment (PT), no treatment, and a combination of PT and local injection in the 142 patients investigated [19]. Dogramaci et al. [20] compared three different injection techniques on 75 patients and found that all three treatments provided good or excellent (as reported by the patient) outcomes at 6-month follow-up in 92–100% of the patients. The three injection techniques included (1) injection of steroid (triamcinolone) plus a local anesthetic; (2) injection of local anesthetic alone with the so-called 'peppering' technique (i.e. multiple local injections consisting of withdrawing slightly after each injection, moving the needle, injecting again without emerging from the skin); and (3) injection of steroid (triamcinolone), a local anesthetic plus the 'peppering' technique. While the authors' conclusion was that the peppering technique combined with corticosteroid injections and local anesthetic produced better clinical results in patients with lateral epicondylitis, a close look at their results revealed that although there was a statistically significant difference between two of the treatment groups, this difference was so small as to be not clinically relevant. Patients in all three treatment groups reported a value of less than 1 on the VAS at 6-month follow-up.

Further complicating this issue is the study by Lindenhovius et al. [21] on 64 patients with lateral epicondylitis. Their RCT looked at two different treatments, either an injection with a corticosteroid or a 'placebo' injection of 1% lidocaine. They found that the corticosteroid injection (dexamethasone) did not improve the apparently self-limiting course of lateral epicondylitis compared to the placebo injection. However, it can be questioned whether or not a local anesthetic is actually a true placebo, especially in light of previous research in the spine and shoulder suggesting that patients may respond equally well to local anesthetic injections as compared to steroid injections [15, 22, 23].

The evidence to date suggests that injections for lateral elbow pain appear to be successful for short-term pain relief, but may be worse for long-term functional outcomes. Comparison to less invasive forms of treatment needs further exploration.

Wrist and hand

Corticosteroid injections for rheumatoid arthritis, juvenile idiopathic arthritis or other inflammatory arthropathies is fairly well established [7–10, 25], but not discussed in detail in this article. The mean duration of remission has been reported as 23.1 months [24], with the additional use of wrist splints providing no increased therapeutic benefit [10].

Carpal tunnel syndrome

The recent Cochrane review of local corticosteroid injections for carpal tunnel syndrome [26] compared these local injections with local placebo injections, systemic steroid injections or other non-surgical treatments and found 12 studies that met their inclusion criteria for review. Corticosteroid injections were superior to placebo injections, oral corticosteroids, or systemic corticosteroid injections for up to 1 month post treatment. However, local corticosteroid injection does not improve outcomes compared to either anti-inflammatory treatment combined with wrist splinting after 8 weeks or compared to Helium-Neon laser treatment after 6 months. Additionally, more than 1 local injection does not add any clinical benefit.

While a few studies support the use of splints for carpal tunnel syndrome, patient compliance with this treatment appears to be a problem. Therefore, the use of a single local corticosteroid injection in the short-term management of carpal tunnel syndrome is supported, with patients strongly encouraged to use night splints for long-term management [27].

Stenosing tenosynovitis including de Quervain's disease

The best evidence available addressing this issue is a pooled quantitative literature evaluation including 459 wrists done in 2003 [28]. The studies were descriptive and compared patient outcomes before and after treatment, or RCTs comparing one treatment method with another. The conclusions were that the best treatment for stenosing tenosynovitis is corticosteroid injection alone, with an 83% cure rate. The cure rate for this treatment, (defined as a complete resolution of symptoms), appears to far exceed other therapeutic modalities such as injection plus splint, splint alone, rest or NSAIDs. Two RCTs were also found on this topic, but both studies used corticosteroid injections (triamcinolone) as a treatment for all patients, only randomizing patients to receive various additional therapies as well as the corticosteroid injection [29, 30]. The conclusions from these RCTs are that supplementing patients with oral NSAIDS or adding an extra drug to reduce 'flare reactions' (delayed post-injection transient increase in pain) has no benefit over corticosteroid injections alone. Between 67 and 68% of patients reported substantial improvement after a single injection at 3-week follow-up and 95% of patients were improved, (including up to 4 injections), at approximately 1-year follow-up.

Improvement was defined as complete resolution of tenderness over the radial styloid process, complete resolution of pain with resisted thumb abduction and extension, a negative Finkelstein test and at least 90% improvement in the pain score.

Wrist/hand: osteoarthritis of the first carpometacarpal joint

While no systematic reviews or meta-analyses were found for most individual joints in the hand or wrist, two RCTs looked at osteoarthritis of the first carpometacarpal (CMC) joint, a common target site for this condition [31, 32]. Both studies compared hyaluronic acid as a therapeutic injectate to corticosteroids in a total of 80 patients. The results demonstrate that both drugs are effective, although different corticosteroids were used in each of the studies (triamcinolone or methylprednisolone acetate). The steroids showed a faster onset of pain relief with a maximum effect at 2 and 3 weeks after initiation of treatment. Hyaluronic acid seemed to be the better choice with slight to moderate superiority in almost all of the assessed clinical parameters (pain relief, lateral pinch (key grip) strength, pulp pinch power, radial abduction, swelling, heat) after 6 months. Patients injected with hyaluronic acid reported a 56% decrease in the VAS score at 26 weeks compared to only a 22.6% decrease in the VAS for patients injected with the corticosteroid [31].

Lower extremity

Hip osteoarthritis

Although therapeutic injections into the hip joint have been used for many years, no systematic reviews or meta-analyses were found. Three fairly recent prospective, double-blinded RCTs [33–35] were done however. The most recent of these RCTs involved 52 patients with randomization into either a corticosteroid or a placebo injection (bipuvicaine) group [35]. Clinically meaningful improvements in the Western Ontario and McMaster Universities OA Index (WOMAC) score were reported by the corticosteroid group, with 49.2% of patients experiencing at least a 50% reduction in their pain score compared to only 2.5% reduction for the placebo group. These effect differences lasted at least 2 months. Another larger RCT by Kullenberg et al. [34] with similar results looked at hip OA patients who experienced pain at rest as well as upon weight bearing for at least the previous 4 weeks. Two groups were compared with 40 patients receiving an imaging-guided injection of corticosteroid into the hip while the other 40 patients received a local anesthetic into the hip. Several outcome measures were evaluated with a follow-up of 12 weeks. All outcome measures demonstrated significant improvement for the corticosteroid group of patients, particularly pain at rest with >50% improvement on the VAS at 3 weeks post injection. Range of motion significantly improved in all directions, particularly in internal rotation, but no specific numbers were provided. There was no significant improvement in pain or functional ability in the patients treated with anesthetic. The last of these three RCTs compared corticosteroid injections into the hip joint with hyaluronic acid (HA) and placebo (saline) injections and found that corticosteroids were superior to either of the other two injections, particularly at 2 weeks and for 'pain on walking', but the effect was short lived and gone by the 3 month follow-up. The conclusion of that study is that steroids are good for acute flair-ups of osteoarthritis and rheumatoid arthritis.

An older prospective cohort study [36] compared osteoarthritis and rheumatoid arthritis patients for their response to corticosteroid injections into the hip. Once again, the effects were significant pain relief, particularly night pain, but only for short periods of time. No difference in pain relief between osteoarthritis and rheumatoid arthritis patients was observed, but patients with a more hypertrophic form of arthritis experienced significantly more pain relief compared to patients with an atrophic (associated with chondrocalcinosis and more rapid progression) form.

Based on these studies, it appears that corticosteroid injections into the hip do provide short-term improvement in pain and function (2–3 months), particularly for night pain, but that they are not effective for long-term pain relief. Side effects may occur and have to be taken into consideration. Osteonecrosis of the femoral head is a known side effect of particularly oral corticosteroids, but may also occur with joint injections, and there is the additional question as to whether or not steroid injections may further increase the damage to articular cartilage [37].

The injection of hyaluronic acid and similar compounds, also known as viscosupplementation, into the joints of patients suffering from osteoarthritis, particularly in the knee, is receiving increasing attention. The goal of treatment is not only relief of symptoms, but perhaps improvement in the articular cartiligenous structure. The use of viscosupplementation in the hip is not as substantiated however. One recent systematic review, published in 2008 [38], evaluated the level of evidence in support of this treatment. While 16 articles were included in this review, with a total of 509 patients, the quality of the included studies (according to the principles of evidence-based medicine) was not such that definitive conclusions could be made. Thus, the impression is that viscosupplementation, performed using imaging guidance, seems an effective treatment for patients with hip OA, but at this point in time, cannot be recommended as standard therapy until more studies are done.

Knee osteoarthritis

More evidence is available for therapeutic injections into the knee than for any of the other peripheral joints. The best evidence is contained in three recent systematic reviews evaluating both corticosteroid and viscosupplementation injections for patients with osteoarthritis as well as a meta-analysis of viscosupplementation for OA patients [39–42]. The evidence supporting the use of corticosteroid injections for patients with OA is well established for short-term benefits, but as in other joints, longer-term benefits are not confirmed [39]. The corticosteroid triamcinolone hexacetonide was superior to betamethasone for pain reduction up to 4 weeks with the relative risk (RR) of 2.00 (95% confidence interval 1.10–3.63).

The evidence supporting the use of viscosupplementation using hyaluronan and hylan products demonstrates that this is an effective treatment for OA of the knee with improvement of pain, function and patient global assessment, particularly pain on weight bearing at 5–13 weeks after injection [40–42]. Patients' pain levels decreased by around 50% while their function improved from 9% at baseline to 32% during the 5–13 weeks after injection. There appears to be considerable variation between products [42]. Comparing corticosteroid injections with viscosupplementation injections consistently shows that the hyaluronic acid products, while slower in onset of action, have a more prolonged effect compared to the corticosteroids [39, 40].

Ankle and foot

Little published evidence supporting the use of therapeutic joint injections currently exists for the foot and ankle region. There are no systematic reviews or meta-analyses. The only RCT found for the ankle region compared a local anesthetic to saline for the relief of ankle pain after an arthroscopic procedure [43]. A small but prospective cohort study followed 18 patients (36 joints) who had either OA or RA for 1 year using a validated, region specific questionnaire, after intra-articular corticosteroid injection [44]. This study found a statistically significant improvement up to 6 months post-injection, with those patients showing the most improvement at 2 months also having the most beneficial response at 1 year. However, in general, maximal improvement was at 4 weeks, similar to studies on other joints, and declined over time. The use of viscosupplementation was also investigated in 75 patients with OA of the ankle in one prospective clinical trial (not RCT) with a 6-month follow-up [45]. After 5 weekly injections most patients experienced significant improvement in both pain and function, starting as early as 1 week after the fifth injection, with 86.7% of patients reporting satisfaction with treatment at 6 months. Adverse events were rare and all outcome measures other than range of motion (ankle osteoarthritis scale, American orthopaedic foot and ankle society ankle/hindfoot scores, patients' global satisfaction) improved.

First metatarsophalangeal joint

A well-designed RCT, using a placebo control group, is planned to evaluate the efficacy of viscosupplementation for treatment of OA involving the first metatarsophalangeal (MTP) joint of the foot [46]. However, this trial has not been completed and thus data is not available. A previously performed RCT comparing viscosupplementation with intra-articular corticosteroid injection to this same joint found that while both injectates produced significant improvements in pain at rest, pain with palpation and pain on passive mobilization, only the patients receiving hyaluronate (viscosupplementation) had decreased pain with walking. As in other studies evaluating hyaluronate, the positive effects of treatment were longer lasting for viscosupplementation compared to corticosteroids [47]. The VAS score for the viscosupplementation group decreased from a mean baseline score of 62.2–26.2 mm at day 84, while the corticosteroid group decreased from a mean baseline score of 58.7–34.1 mm at day 84. Therefore, the current evidence suggests that there is a role for both corticosteroid and viscosupplementation injections into the first MTP joint of the foot, but the effects are more enduring with hyaluronate.

Possible weaknesses of evidence-based medicine

There is some debate whether or not RCTs (which then lead on to systematic reviews and meta-analyses) should be the gold standard for research into interventional pain medicine techniques [44, 48], especially from an ethical perspective. Large well-designed prospective observational studies may more closely resemble the actual patient population, making the evaluation of subgroups more feasible [48]. One can argue that perhaps RCTs should not be the only evidence used in systematic reviews to evaluate the effectiveness of interventional pain therapies. Furthermore, research studies reporting patient outcomes for interventional therapies should be easy to interpret and should assist the radiologist or clinician to explain expected results to patients [49, 50]. Reporting of p values may not be optimal for this purpose. The proportion of patients who significantly improve with treatment, confidence intervals as well as the 'numbers needed to treat' are more appropriate statistics to report [49, 50]. Easily understood research results, such as the percentage of patients who significantly improve with a particular therapeutic injection, should lead to more appropriate referrals, optimal injection technique and better outcomes for the patients.

Conclusions

With the exception of the knee, possibly the hip and patients with inflammatory arthropathies, additional research evidence is required regarding the use of therapeutic joint injections from the point of view of evidence-based medicine. However, for most of the peripheral joints, including the shoulder, current evidence looks promising based on cohort studies and cross-sectional studies. Controversy exists in some areas as to whether or not corticosteroids provide better outcomes compared to local anesthetic injections alone. In some joints, viscosupplementation may provide more prolonged improvement, with corticosteroids good for short-term relief.

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